OPTIMIZATION OF DRUGS'ACTION USING MINIMIZATION METHODS

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Abstract. This paper deals with optimal therapeutics defined from mathematical models of drugs'action. For obtaining the optimum doses and times analytic and numerical methods are proposed. An original optimization technique giving the global optimum will be described. The basic idea consists to use a space filling curve.

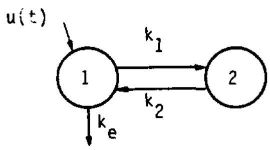
Keywords. Optimization; optimal control; biomathematics; pharmacokinetics; modelling.

INTRODUCTION

Mathematical modelling plays a great role in biology and medicine. Its main utility is the possibility to act on systems by mean of control variables. When applied to the dynamics of drugs using of optimization or optimal control techniques allows to define optimal doses in function of time. First we shall consider optimal control problem associated to linear compartmental models. In that case it is possible to calculate the optimal solution with analytical methods. In more complex cases, non linear models are necessary and their optimization according to some criterion needs more complicated techniques involving numerical methods such as dynamic programming (Bellman-Dreyfus,1962) or non linear minimization methods (Bellman,1983), (Kalaba-Spingarn,1982). A new global minimization method (Cherruault-Guillez,1985) will be described and applied to pharmacodynamic problems (Wagner,1975). The concrete result involved by using all these mathematical methods is a better efficacy of drugs and therapeutics. It is an important assistance for pharmacologists and physicians. A systemic approach is absolutely necessary for studying complex regulated phenomena.

OPTIMIZATION OF LINEAR COMPARTMENTAL MODELS

Linear compartmental model are very popular in biology and medicine (Bellman,1983), (Cherruault,1983) (Jacquez,1972). They allow to modelize biochemical systems depending only on time. Furthermore they are simple to obtain because their equations are obtained by making a mass balance (Jacquez,1972). In spite of their simplicity compartmental models may be adapted to various situations (linear or not) by modifying the exchange hypothesis (Gibaldi-Perrier,1975). Consider a drug that satisfies a linear compartmental model such as the following (often used in pharmacokinetics). Fig.1.



(Fig.1)

where 1 is the blood compartment and 2 may be the action compartment. A differential system can be associated to this model by making a mass balance and using the hypothesis : the quantity (by time unit) going from compartment i to compartment j is proportional to the quantity $x_i(t)$ contained in the compartment i. This involves :

$$\begin{cases} \dot{x}_1 = -(k_1+k_e)\, x_1 + k_2\, x_2 + u(t) \\ \dot{x}_2 = k_1\, x_1 - k_2\, x_2 \\ x_1(o) = x_2(o) = 0 \quad \text{fixed initial conditions} \end{cases} \tag{2.1}$$

where u(t) is an input function (control variable) which can be controled and chosen so that a given criterion be optimized. These assertions will become clearer in the following. As can be seen on fig. 1, u(t) is introduced in the first compartment. An optimal control problem may now be set : Maintain a given quantity a (fixed) in the first compartment by choosing a convenient function u(t).

Mathematically the problem is the following :

$$\begin{cases} \text{Find } u(t) \text{ such that :} \\ \int_o^\infty (x_1(t) - a)^2\, dt \quad \text{be minimum according to } u \text{ and with constraints (2.1)} \end{cases} \tag{2.2}$$

This is an optimal control problem that is to say a special case of optimization problem.

Our criterion $\int_o^\infty (x_1(t) - a)^2\, dt$ has to be minimized according to a function u(t) implicitly contained in the functional. First we shall describe an analytic technique giving a global minimum of our criterion. Let us solve the particular problem (2.2), (2.1) with initial conditions.

$$x_1(o) = a \;,\; x_2(o) = 0 \tag{2.3}$$

Now we try to realize $x_1(t) \equiv a$ $(t \geq o)$ giving a global minimum for (2.2).

The second equation (2.1) may be integrated and gives :

$$x_2(t) = -\, a\, (k_1/k_2)(e^{-k_2 t} - 1) \tag{2.4}$$

Then the first equation (2.1) leads to the optimal solution for u(t) :

$$u(t) = a\, (k_e + k_1\, e^{-k_2 t}) \tag{2.5}$$

The general problem (2.1), (2.2) with initial conditions $x_1(o) = x_2(o) = o$ can be solved by using the Laplace transformation. It is easy to verify that the general problem with $u(t) = a\ \delta_{(o)} + u_1(t)$, where $\delta_{(o)}$ is the Dirac mass (Schwartz,1966) at time 0 and $u_1(t)$ is a classical function, admits a solution with $u_1(t)$ solution of (2.1), (2.2) with initial conditions $x_1(o) = a$, $x_2(o) = 0$. Therefore the general solution of our control problem is a distribution function given by :

$$u(t) = a\ (\delta_{(o)} + k_e + k_1\ e^{-k_2 t}) . \qquad (2.6)$$

Of course the solution (2.5) corresponding to a particular case may be found by using the Laplace transformation. Generalization to n compartments with an input u(t) in the first compartment and a criterion involving the same compartment does not present any difficulty. The optimal control u(t) will be a linear combination of δ, 1, $e^{-\lambda_i t}$, $i = 1,\dots, n-1$, where the λ_i are calculated from the exchange parameters k_j.

Furthermore more general criteria could be considered. With the same model (fig.1), translated by the differential system (2.1), and the criterion :

$$\underset{u(t)}{\mathrm{Min}} \int_0^{\infty \text{ or } T} g(x_1(t))\ dt \ , \text{ g given function, the optimal control is easily found.} \qquad (2.7)$$

Indeed, we first solve $\underset{x_1(t)}{\mathrm{Min}} \int_0^{\infty} g\ (x_1(t))\ dt$

giving the optimal solution $x_1^*(t)$.

Then putting x_1^* in the second equation (2.1) gives x_2 optimal then the first equation (2.1) furnishes the optimum function u(t). Now let be a more complicated situation with the criterion :

$$\underset{u(t)}{\mathrm{Min}} \int_0^{T} g(x_1(t), u(t))\ dt \ , \ g \geq 0. \qquad (2.8)$$

The resolution of

$$\underset{u}{\mathrm{Min}}\ (g(x_1, u)) \qquad (2.9)$$

by a numerical technique leads to the optimal function (by using for instance the results of § 3) :

$$u = u(x_1) \qquad (2.10)$$

Putting (2.10) into the differential system (2.1) leads to explicit or numerical solutions for $x_1(t)$ and $x_2(t)$. The optimum function u(t) is then deduced from the first equation (2.1). We can generalize the previous method to more general criteria. For instance it is possible to consider :

$$\underset{u}{\mathrm{Min}} \int_0^{T} g\ (x_1, x_2, u)\ dt \quad \text{or} \qquad (2.11)$$

$$\underset{u}{\mathrm{Min}} \int_0^{T} g\ (x_1, x_2, u, t)\ dt$$

(2.11) leads to a function u depending on x_1 and x_2 and also of t in the second case. The Alienor transformation (Cherruault-Guillez,1983) may be used for reducing the variables x_1, x_2 to a single variable θ . This process will be described and used in a global optimization technique developed in MEDIMAT laboratory.

ALIENOR OR A GLOBAL MINIMIZATION METHOD (Cherruault-Guillez,1983)

Many systems in biology or medicine lead to identification or optimization problems. Their resolution needs to use algorithms of minimization. Most of them (Swan,1984) give only local minimum and need the existence of some derivatives. The technique described below may be applied to continuous functions. It is based on a space filling curve. More precisely consider a two variables function to minimize.

$$\underset{x,y}{\mathrm{Min}}\ \ f(x,y) \text{ . Setting} \qquad (3.1)$$

$$x = a\theta\cos\theta \ , \ y = a\theta\sin\theta \ , \ \theta > o \ , \qquad (3.2)$$

we obtain a new optimization problem according to θ

$$\underset{\theta}{\mathrm{Min}}\ \ f\ \ (a\theta\cos\theta \ , \ a\theta\sin\theta) = \underset{\theta}{\mathrm{Min}}\ \ G(\theta) \qquad (3.3)$$

where $G(\theta) = f\ (a\theta\cos\theta \ , \ a\theta\sin\theta)$

It is easy to prove (Cherruault,1983) that the optimum θ^* leads to $x^* = a\theta^*\cos\theta^*$, $y^* = a\theta^*\sin\theta^*$ converging towards the set (x^+, y^+) realizing the minimum of f(x,y). Of course θ may be deduced from (x,y) by the relation :

$$\theta = (1/a)\ (x^2 + y^2)^{1/2} \qquad (3.4)$$

This method is based on the properties of the Archimed's spiral $r = a\theta$ giving an approximation of the Peano's curve when $a \to o$.

The generalization to n variables is very easy (Cherruault-Guillez,1985). This method, called Alienor, can also give all the maximums or minimums of a n-variables function. Moreover it may be used for approximating n variables functions and consequently for solving partial differential equations.

OPTIMIZATION OF NON LINEAR COMPARTMENTAL MODELS

Consider the non linear compartmental model (2 compartments) represented by the differential system (Gibaldi-Perrier,1975), (Jones-Sleeman,1983)

$$\begin{cases} \dot{x}_1 = g(x_1) + k_{21}\ x_2 + u(t) \ , \ g \text{ non linear function} \\ \dot{x}_2 = k_{12}\ x_1 - k_{21}\ x_2 \\ x_1(o) = a \ , \ x_2(o) = o \end{cases} \qquad (4.1)$$

The associated control problem will be :

$$\underset{u(t)}{\mathrm{Min}} \int_0^{\infty} (x_1(t) - a)^2\ dt \qquad (4.2)$$

- A first analytic method consists to take $x_1(t) \equiv a$, $t > o$ and to carry back this value in the second equation (4.1). We obtain :

$$x_2(t) = -a\ (k_{12}/k_{21})\ (e^{-k_{21} t} - 1) \qquad (4.3)$$

and thus the optimal solution u(t) of (4.2), (4.1) is given by :

$$u(t) = -g(a) + a\,k_{12}\,(e^{-k_{21}t} - 1) \qquad (4.4)$$

Of course it is a generalization of the method described in the linear case. More general systems may be considered as for instance :

$$\begin{cases} \dot{x}_1 = f_1\,(x_1,\dots,x_n) + u(t) \\ \vdots \\ \dot{x}_n = f_n\,(x_1,\dots,x_n) \\ x_1\,(o) = a\ ,\ x_2(o) = \dots = x_n(o) = 0 \end{cases} \qquad (4.5)$$

Putting $x_1(t) \equiv a$ in (4.5) allows to solve the (n-1) last differential equations according to x_2, $x_3,\dots, x_n$. Then the optimal control u(t) is given explicitly by the first equation (4.5).

$$u(t) = -\,f_1\,(a\ ,\ x_2\ ,\dots,\ x_n) \qquad (4.6)$$

the functions $x_2(t),\dots, x_n(t)$ being previously calculated (numerically).

Note that more general initial conditions may be introduced. If we have $x_1(o) = x_2(o) = \dots = x_n(o) = o$ then the term a $\delta_{(o)}$ has to be added to the optimal solutions (4.4) and (4.6).

- The second method is based on a linearization technique. Coming back to the differential system (4.1) a Taylor's development of order 1 leads to

$$\begin{cases} \dot{x}_1 = g(x_1(o))+(x_1(t)-x_1(o))g'(x_1(o))+k_{21}x_2+u(t) \\ \dot{x}_2 = k_{12}\,x_1 - k_{21}\,x_2 \end{cases} \qquad (4.7)$$

on the interval (o, h) , h small.

As previously $x_1 \equiv a$ for $t \in (o, h)$ gives $x_2(t)$ by the same formula

$$x_2 = -(a\,k_{12}/k_{21})\left[e^{-k_{21}t} - 1\right]$$

and the first equation (4.7) involves ;

$$u(t) = -g\,(a) - k_{21}\,x_2 \qquad (4.8)$$

On the second interval (h, 2 h) a Taylor's development gives the same solution and so on ...

In this particular case one obtain the same solution as that given by the first method. Generalization to a system of n non linear equations according to $x_1,\dots, x_n$ but linear according to u(t) which appears only in the first equation is possible without difficulty. A more general situation may arise. For instance consider the optimal control problem :

$$\underset{u(t)}{\text{Minimize}} \int_0^T g\,(\vec{x}(t)\ ,\ u(t))dt\ ,\ g \text{ given} \qquad (4.9)$$

where the vector $\vec{x}(t) = (x_1(t),\dots, x_n(t))$ and the function u(t) are solutions of the non linear compartmental model :

$$\begin{cases} \dot{x} = f\,(x_1,\dots, x_n,\ u,\ t) \\ \vec{x}(o) = \vec{x}_o \text{ fixed} \end{cases} \qquad (4.10)$$

and where the model f is supposed identified (known).

First the Alienor transformation is used for connecting $x_1,\dots, x_n$. These variables are transformed into a single variable θ(t).

$$(x_1,\dots, x_n) \longrightarrow \theta \qquad (4.11)$$

Then we solve (numerically) the optimization problem giving the optimal solution :

$$\text{Min}\ \ g\,(x,u,t) \qquad (4.12)$$

$$u = u\,(\theta,t) \text{ or } u = u(\vec{x},t) \qquad (4.13)$$

owing to the Alienor transformation and its inverse.

Putting (4.13) in (4.10) leads to the numerical resolution of a differential system. One obtain the optimal functions $x_1,\dots, x_n$ and then the u optimal by using (4.13).

Generalization to a control vector $\vec{u}(t)=(u_1(t),\dots, u_m(t))$ is theoritically possible but involves many supplementary calculus.

Remark

When the control scalar function u(t) arises in a non linear fashion in the state system (as in (4.10) for instance) a Taylor development of order 1 may be used. The first analytic method of this paragraph can be performed on each interval of linearization $[t_i,\ t_{i+1}]$.

- Another suitable method consists to look for an approximation of the (measured) observation (generally the measure of one compartment) in function of the absorbed or injected dose (Wagner,1975).

Let be x(t) a measured function corresponding for instance to a blood concentration. It is always possible to represent numerically x(t) by a linear combination of exponentials :

$$x(t)= \sum_{i=1}^{n} a_i(D)\, e^{\lambda_i(D).t}\ ,\ \lambda_i(D) < 0 \qquad (4.14)$$

where the coefficients a_i and λ_i must be identified from experimental data in function of the administred dose. Alienor method is well adapted for solving this identification problem.

Then an optimization problem may be set as follows :

> Find doses and times of administration such that the criterion
>
> $$J = \int_0^\infty [\ x(t) - A\ ]^2\ dt \text{ be minimum} \qquad (4.15)$$

The constant A in (4.15) is chosen from medical considerations. Of course the function x(t) in (4.15) has to be precised because it is associated to multiple doses D_j (j = 1,.., m) given at times t_j. If x(t) is a concentration, a quantity or an effet one admits generally (Gibaldi-Perrier,1975) the additivity of the outputs corresponding to successive doses. This hypothesis yields the following relation :

$$x(t)= \sum_{j=1}^{m} Y(t-t_j) \sum_{i=1}^{n} a_i(D_j)e^{\lambda_i(D_j).(t-t_j)} \qquad (4.16)$$

where Y(t) is the Heaviside function (=1 if t>0 , 0 if t < 0) .

Putting (4.16) into the criterion J of (4.15) yields a classical non linear optimization problem:

Min J according to the t_j an D_j (given at time t_j) where the unknown parameters t_j, D_j appears explicitly in the functional J. (4.17)

But J is not linear therefore the use of a method such that Alienor is well adapted for finding the global minimum. The dynamic programming technique (Bellman-Dreyfus, 1962) can also be performed and is convenient for the problem (4.15), (4.16). The resulting optimal solution will be a linear combination of Dirac masses :

$$u(t) = \sum_{j=i}^{m} D_j \, \delta_{(t_j)} \tag{4.18}$$

If necessary such a distribution function u(t) can be approximated by an ordinary function. A piecewise constant function may be convenient as well as a continuous function (Schwartz, 1966). In some pharmacologic problems the drug effect is measured in the same time than the blood concentration. An a priori mathematical functional relation may be tested. When considering for instance a concrete drug such as Tertatolol the following model was performed after many trials (Wagner, 1975).

$$E(t) = b_o + b_1 \, \mathrm{Log}\,(1 + C(\gamma_D(t))). \tag{4.19}$$

b_o is a constant depending on the individual ; b_1 (independent of the absorbed dose D) and the function $\gamma_D(t)$ have to be identified from experimental data. These data are the measure of concentrations C and effects during time and for various dose D_j, $j = 1,\dots,m$. Such a formula is suggested by the classical literature (Gibaldi-Perrier, 1975), (Wagner, 1975) where only Log. linear relations are considered.

A control optimal problem may be set as follows :

$$\underset{D_j,t_j}{\mathrm{Min}} \int_o^T (E(t) - M)^2 \, dt \quad j=1,\dots,m \tag{4.20}$$

where M is a constant fixed from medical considerations.
The definition of E(t) on the interval (0,T) is similar to that given in the previous paragraph for x(t) (formula 4.16).

A non linear minimization problem arises that may be solved by a numerical method such as for instance the Alienor's method or the dynamic programming technique. The identification of a formula such as (4.19) needs less informations about the biological system. Note that a recent paper (Takada-Yoshikawa-Muranishi, 1985) uses almost the same idea without deducing conclusions about an optimal therapeutics.

NUMERICAL APPLICATIONS

The previous methods were applied to problems associated to pharmacologic drugs such as tertatolol which is studied by Servier laboratories. For instance the global optimization technique Alienor was performed for the problem.

$$\underset{\substack{D_o,\dots,D_j \\ t_1,\dots,t_j \\ t_o = o}}{\mathrm{Min}} \int_o^T (E(t) - M)^2 \, dt \tag{5.1}$$

Taking j = 2, T = 72 h, M=19 involves the optimal values

$$D_o=8.07,\ t_o=0,\ D_1=1,\ t_1=38.69 \text{ h}, \quad D_2=5.3,\ t_2=51.84 \text{ h}. \tag{5.2}$$

With j = 2, T = 72, M = 20 in (6.1) one obtained :

$$D_o=6.895,\ t_o=0,\ D_1=1,\ t_1=43.56, \quad D_2=1,\ t_2=58.89 \text{ h}. \tag{5.3}$$

When using a dynamic programming technique for solving :

$$\underset{D_o,\dots,D_j}{\mathrm{Min}} \sum_{i=0}^{m} \int_{t_i}^{t_{i+1}} (E(t) - 20)^2 \, dt$$

with t_i fixed such that $t_{i+1} - t_i = 24$, $t_o = 0$, the calculated doses were the following :

$$D_o=4.69,\ D_1=4.53,\ D_2=4.52,\ D_3=4.67 \quad t_o=0,\ t_1=24 \text{ h},\ t_2=48 \text{ h},\ t_3=72 \text{ h} \tag{5.4}$$

Many other results are available in technical reports of MEDIMAT laboratory.

CONCLUDING REMARKS

The present literature is very poor in papers treating of optimization in biology. Some too scarce attempts exist (Swan, 1984) but they consider generally the linear case. Our aim was to treat mainly the non linear case and to give some simple and efficient numerical methods for solving optimal control problems. We saw that optimization allows to act on the biological system by minimizing some optimal criterion. Therefore optimal policies may be defined as for instance when using some drugs. In that case doses and times of absorption may be mathematically calculated. In some cases an analytic solution is available while in other cases only a numerical solution can be proposed. In our study the numerical optimization methods play a great role and specially an original technique based on a "space filling curve" idea.

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